REMARKS

Claims 1-20, 22-29, 31, and 32 are pending in the application. Claims 1, 17, 18, 20, 29, and 31 have been amended, and claims 21 and 30 have been canceled without prejudice. Support for the amendments and can be found in original claim 21 and in the specification at, e.g., page 2, lines 7-13; page 5, lines 26-29; page 10, lines 5-31; and page 12, lines 9-28. These amendments add no new matter.

35 U.S.C. §102(e) (Anticipation)

At pages 3-4 of the Office Action, the Examiner rejected claims 1, 3-6, 8, 17, 19, 20, 23-26, 29, and 32 as allegedly anticipated by Vernachio et al., U.S. Patent No. 6,462,254 ("Vernachio"). According to the Examiner,

> Vernachio et al. teaches methods of isolating and concentrating a fusion protein which comprises a capture tag and a detection tag comprising administering to a mammal a nucleic acid encoding a fusion protein comprising a capture tag sequence and a detection tag sequence and capturing the fusion protein from a sample from the mammal with an antibody that specifically binds to the capture tag sequence (Vernachio et al., columns 4, 7, and 13-14, see claims 1-15). The capture tag sequence is the "second amino acid sequence" of the fusion protein and the "first member of a specific binding pair", while the antibody which recognizes the capture tag is the "second member of the specific binding pair". Vernachio et al. further teaches that the capture tag can be a peptide more than 5 amino acids long, see column 14, claim 3; and that the antibody can be a monoclonal antibody, see column 5, lines 51-56). Vernachio et al. also teaches the immobilization of the fusion protein to a solid surface such as a membrane, microtiter dish, or magnetic bead (Vernachio et al., column 6, lines 57-67). In addition, Vernachio et al. teaches that the sample from the mammal containing the fusion protein can be serum or a tissue lysate (Vernachio et al., column 11, lines 28-37, and column 12, lines 25-67). Finally, Vernachio et al. teaches that the purified fusion protein can be used in binding assays with antibodies which recognize and bind to detection tag sequence present in the fusion protein (Vernachio et al., columns 7-8 and 13-14, see in particular claim 4). Thus, by teaching all the elements of the claims as written, Vernachio et al. anticipates the instant invention as claimed.

Applicants respectfully traverse the rejection in view of the claim amendments and the following comments.

Amended independent claim 1 is directed to a method of screening to identify target binding molecules that bind to an amino acid sequence. The method requires the expression of a fusion protein (containing a "first amino acid sequence" and a "second amino acid sequence") in a mammal, the removal of the expressed fusion protein from the mammal, and the binding of a member of a specific binding pair to the second amino acid sequence. Subsequently, the first amino acid sequence of the fusion protein is contacted with a collection of candidate target binding molecules and one or more target binding molecules from the collection is identified as binding to the first amino acid sequence.

Vernachio describes methods for isolating and detecting recombinantly produced fusion proteins. The fusion proteins described by Vernachio contain (1) a "capture tag sequence" (which is used to isolate the fusion protein from a complex mixture), (2) a "detection tag sequence" (which is used to detect expression of the fusion protein), and (3) a "polypeptide sequence of interest" (which can be essentially any polypeptide, such as a therapeutic protein used in gene therapy).

The capture and detection tag sequences of Vernachio function merely as means for determining whether the "polypeptide sequence of interest" is present in a cell or animal following administration of a nucleic acid encoding the fusion protein to the cell or animal (e.g., a means for confirming that a recombinant protein for a gene therapy protocol has been expressed in a mammal). In detecting the presence of the fusion protein, Vernachio contacts the fusion protein (which is isolated via the capture tag sequence) with a specific antibody that is known beforehand to bind to the detection tag sequence.

Vernachio does not describe methods of screening to identify molecules that bind to its "polypeptide sequence of interest," its "detection tag sequence," or any other component of its fusion protein. Instead, Vernachio contacts its isolated fusion protein with only a single antibody that has been characterized beforehand for its ability to bind the detection tag sequence. The presence or absence of a signal indicating that the antibody has bound to the detection tag

sequence is used as an indicator of whether or not the fusion protein is present in the sample. Vernachio does not describe contacting its fusion protein or any component thereof with a collection of candidate target binding molecules, as is required by the method of claim 1. Accordingly, Vernachio does not anticipate the screening method of claim 1 or claims 3-6, 8, 17, and 19 that depend therefrom.

Amended independent claim 20 is directed to a method of preparing a purified protein. The method requires the expression of a fusion protein (containing a "first amino acid sequence" and a "second amino acid sequence") in a mammal, the removal from the mammal of a biological sample containing the expressed fusion protein, and the binding of a member of a specific binding pair to the second amino acid sequence. Subsequently, components of the biological sample that are not bound to the second member of the specific binding pair are removed (e.g., by washing) and the first amino acid sequence is then cleaved from the second amino acid sequence. The liberated first amino acid sequence can then be used, for example, in screening assays to identify compounds that bind to the amino acid sequence.

Vernachio does not describe cleaving the capture tag sequence from other components of a fusion protein. Such a cleavage step is not a component of the methods of Vernachio since Vernachio is interested in purification of the fusion protein only as a means of detecting whether the protein is actually present in a sample. Vernachio has no interest in cleaving its "polypeptide sequence of interest," its "detection tag sequence," or any other component of the fusion protein from the capture tag sequence, as such a cleavage step would be inconsistent with Vernachio's method of detecting an intact immobilized fusion protein. Accordingly, Vernachio does not anticipate the method of claim 20 or claims 23-26, 29, and 32 that depend therefrom.

35 U.S.C. §103(a) (Obviousness)

At pages 5-8 of the Office Action, the Examiner rejected claims 2, 10, 11, 18, 21, 22, 27, 28, 30, and 31 as allegedly unpatentable over Vernachio in view of Lo et al., U.S. Patent No. 5,726,044 ("Lo"). According to the Examiner,

> Vernachio et al. differs from the instant invention by not teaching that the capture tag sequence is an Fc domain of an immunoglobulin. Vernachio et al. however

teaches that the capture tag is a sequence of amino acids that specifically binds to a ligand such as an antibody (Vernachio et al., column 2, lines 20-21, and column 2). Vernachio et al. further teaches that the particular capture tag sequence is not critical to the invention, and that the capture tag is chosen for its ability to concentrate the fusion protein (Vernachio et al. column 5, lines 11-16). Lo et al. provides motivation for using an Fc region of an immunoglobulin as a "capture tag sequence" in the fusion protein provided by Vernachio. Lo et al. teaches nucleic acid vectors for expressing a fusion protein in mammalian cells wherein the fusion protein comprises an Fc region of an immunoglobulin linked by a protease cleavage site to a selected target polypeptide (Lo et al., columns 3-4). Lo et al. further teaches that the presence of the Fc region of an immunoglobulin in the fusion protein allows for increased production of the target protein and ease of collection because the secreted fusion protein can be collected without the need for cell lysis and can be purified using common reagents including antibodies and protein A (Lo et al., column 2, especially lines 29-35, and column 3, lines 9-23). Lo et al. further teaches the advantages of including the protease cleavage site in the fusion protein because the target polypeptide can be easily separated from the Fc region used to purify the fusion protein (Lo et al., columns 3 and 9). Note as well that Lo et al. teaches that protease inhibitors can also be administered to prevent cleavage of the fusion protein by proteases (Lo et al., column 16). Thus, based on the motivation to include the Fc region of an immunoglobulin and a protease cleavage site in a fusion protein in order to facilitate and improve the purification of the fusion protein as taught by Lo, and based on the teaching of Vernachio et al., that the "capture tag sequence" should be selected based on its ability to concentrate the protein, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the Fc region linked to a protease cleavage site as taught by Lo et al. as the "capture tag sequence" in the fusion proteins taught by Vernachio et al.

Applicants respectfully traverse the rejection in view of the claim amendments and the following comments.

Independent claim 1 is directed to a screening method to identify target binding molecules that bind to a given amino acid sequence. The claimed screening method requires that the "first amino acid sequence" of the fusion protein be contacted with a collection of candidate target binding molecules and that one or more target binding molecules from the collection be identified as binding to the first amino acid sequence.

As detailed above with respect to the anticipation rejection, Vernachio does not describe contacting its fusion protein or any component thereof with a collection of candidate target

binding molecules, as is required by the method of claim 1. Lo does not add what is lacking in Vernachio. Lo describes DNAs produced by recombinant techniques for inducing expression and subsequent secretion of a target protein. Lo provides no suggestion or motivation to modify the methods of Vernachio so as to screen candidate target binding molecules for their ability to bind to a component of Vernachio's fusion protein. Vernachio's method is a *detection method* (for detecting a fusion protein in a sample taken from a cell or animal) and Lo provides no suggestion or motivation that would lead the person or ordinary skill in the art to re-fashion Vernachio's method so as to convert it into a *screening method* wherein a fusion protein produced in a cell or animal is contacted with a collection of candidate target binding molecules and screened to identify those molecules that can bind to the fusion protein. Accordingly, Vernachio and Lo taken alone or in combination do not render obvious claim 1 or the claims that depend therefrom.

Independent claim 20 is directed to a method of preparing a purified protein by recombinantly expressing a fusion protein (containing a "first amino acid sequence" and a "second amino acid sequence") in a mammal and subsequently removing the protein from the mammal and cleaving the first amino acid sequence from the second amino acid sequence.

As detailed above with respect to the anticipation rejection, Vernachio does not describe cleaving the "capture tag sequence" from other components of its fusion protein. Lo does not add what is lacking in Vernachio. In particular, Lo provides no suggestion or motivation to modify the methods of Vernachio so as to cleave the "polypeptide sequence of interest," the "detection tag sequence," or any other component of Vernachio's fusion protein from the "capture tag sequence." The addition of such a cleavage step would run counter to Vernachio's detection method, the operability of which requires the presence of an *intact* fusion protein (Vernachio's "capture tag sequence" immobilizes the fusion protein, the "detection tag sequence" identifies the presence of the fusion protein, and the "polypeptide sequence of interest" carries out its intended function in the cell or animal). Lo would not have suggested or motivated the skilled person to alter Vernachio's method so as to cleave the capture tag, as such a modification would have been inconsistent with the means of operation of Vernachio's

detection method. Accordingly, Vernachio and Lo taken alone or in combination do not render obvious claim 20 or the claims that depend therefrom.

At pages 8-9 of the Office Action, the Examiner rejected claims 9 and 12 as allegedly unpatentable over Vernachio in view of Lo and Felgner et al., U.S. Patent No. 5,703,055 ("Felgner"). According to the Examiner,

> While Vernachio et al. does teach administering the nucleic acid to the animal in order to produce the fusion protein through binding to the detection tag sequence, and further teaches that the target antibody capable of binding the fusion protein can be made by challenging the animal with the detection tag, Vernachio et al. does not specifically teach that the nucleic acid encoding the fusion protein is used to challenge the animal to produce the target antibody (Vernachio et al., column 5, lines 53-56). Felgner et al. supplements Vernachio et al. by demonstrating that nucleic acid immunization with an antigenic polypeptide efficiently produces antibodies specific to the immunizing antigen (Felgner et al., columns 38-39 and 42). Thus, based on the teachings of Vernachio et al. that the target antibody can be made by challenging an animal with the fusion protein, and the teachings of Felgner et al. that nucleic acid immunization with an antigen efficiently produces antigen-specific antibodies, it would have been *prima facie* obvious to the skilled artisan to prepare the target antibodies by immunizing an animal with the nucleic acid encoding the fusion protein as taught by Vernachio et al. or Vernachio et al. in view of Lo et al. with a reasonable expectation of success.

Applicants respectfully traverse the rejection in view of the claim amendments and the following comments.

Vernachio, Lo, and Felgner do not suggest the methods of dependent claims 9 and 12. Felgner merely describes methods of generating antibodies in an animal by the administration of a DNA sequence encoding an immunogen. Felgner provides nothing that supplements the deficiencies of Vernachio and Lo, as discussed above, to render obvious independent claim 1 or dependent claims 9 and 12. Accordingly, once independent claim 1 is held allowable, these dependent should also be in condition for allowance.

35 U.S.C. §112, Second Paragraph (Indefiniteness)

At pages 9-10 of the Office Action, the Examiner rejected claims 17, 18, and 29-31 as allegedly indefinite in their recitation of the phrase "further comprising immobilizing the fusion protein." According to the Examiner, "[t]he claims do not clarify when the fusion protein is immobilized in relation to the steps recited in the parent claims."

Claim 30 has been canceled, thereby rendering its rejection moot.

Claims 17, 18, 29, and 31 have been amended to require that the immobilization of the fusion protein occur: after binding a second member of the specific binding pair to the fusion protein and before contacting the first amino acid sequence with a collection of candidate target binding molecules (claims 17 and 18); or after binding a second member of the specific binding pair to the fusion protein and before removing components of the biological sample that are not bound to the second member of the specific binding pair (claims 29 and 31).

In light of the foregoing claim amendments, applicants respectfully submit that the claims satisfy the definiteness requirement and request that the Examiner withdraw the rejections.

Conclusions

Applicants ask that all claims be allowed in view of the amendments to the claims and the remarks presented herein.

Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13062-002001.

Respectfully submitted,

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